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TITLE: Nematode-extracted serine protease inhibitors and anticoagulant proteins

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US-CL-CURRENT: 530/350

CLAIMS:

We claim:
1. An isolated protein having anticoagulant activity, including factor Xa inhibitory activity, and having one or more NAP domains, where each NAP domain includes the sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 (Formula II), wherein
(a) A1 is an amino acid sequence of 7 to 8 amino acid residues;
(b) A2 is an amino acid sequence;
(c) A3 is an amino acid sequence of 3 amino acid residues;
(d) A4 is an amino acid sequence;
(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;
(f) A6 is an amino acid sequence;
(g) A7 is an amino acid residue;
(h) A8 is an amino acid sequence of 11 to 12 amino acid residues;
(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and
(j) A10 is an amino acid sequence;
wherein each A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid residues and wherein said NAP domain includes the amino acid sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10
wherein
(a) Cys-A1 is selected from SEQ.ID.NOS. 67 and 156;
(b) Cys-A2-Cys is selected from one of SEQ.ID.NOS. 157 to 159;
(c) A3-Cys-A4 is selected from one of SEQ.ID.NOS. 160 to 173;
(d) Cys-A5 is selected from SEQ.ID.NOS. 174 and 175;
(e) Cys-A6 is selected from one of SEQ.ID.NOS. 176 to 178;
(f) Cys-A7-Cys-A8 is selected from SEQ.ID.NOS. 179 and 180;
(g) Cys-A9 is selected from one of SEQ.ID.NOS. 181 to 183; and
(h) Cys-A10 is selected from one of SEQ.ID.NOS. 184 to 186.

2. An isolated protein having anticoagulant activity, including factor VIIa-TF inhibitory activity, and having one or more NAP domains wherein each NAP domain includes the sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 (FORMULA III), wherein
(a) A1 is an amino acid sequence of 7 to 8 amino acid residues;
(b) A2 is an amino acid sequence;
(c) A3 is an amino acid sequence of 3 amino acid residues;
(d) A4 is an amino acid sequence;
(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;
(f) A6 is an amino acid sequence;
(g) A7 is an amino acid residue;
(h) A8 is an amino acid sequence of 11 to 12 amino acid residues;
(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and
(j) A10 is an amino acid sequence;
wherein each of A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid residues, and wherein said NAP domain includes the amino acid sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10
wherein
(a) Cys-A1 is selected from SEQ.ID.NOS. 93 and 205;
(b) Cys-A2-Cys is selected from one of SEQ.ID.NOS. 206 to 208;
(c) A3-Cys-A4 is selected from one of SEQ.ID.NOS. 209 to 222;
(d) Cys-A5 is selected from SEQ.ID.NOS. 223 and 224;
(e) Cys-A6 is selected from one of SEQ.ID.NOS. 225 to 227;
(f) Cys-A7-Cys-A8 is selected from one of SEQ.ID.NOS. 228 to 229;
(g) Cys-A9 is selected from one of SEQ.ID.NOS. 230 to 232; and
(h) Cys-A10 is selected from one of SEQ.ID.NOS. 233 to 235.
3. An isolated protein having serine protease inhibitory activity and having one or more NAP domains, wherein each NAP domain includes the sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 (FORMULA IV), wherein
(a) A1 is an amino acid sequence of 7 to 8 amino acid residues;
(b) A2 is an amino acid sequence;
(c) A3 is an amino acid sequence of 3 amino acid residues;
(d) A4 is an amino acid sequence;
(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;
(f) A6 is an amino acid sequence;
(g) A7 is an amino acid residue;
(h) A8 is an amino acid sequence of 10 to 17 amino acid residues;
(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and
(j) A10 is an amino acid sequence;
wherein each of A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid residues, and wherein said NAP domain includes the amino acid sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10, wherein
(a) Cys-A1 is selected from SEQ.ID.NOS. 96 and 254;
(b) Cys-A2-Cys is selected from one of SEQ.ID.NOS. 255 to 257;
(c) A3-Cys-A4 is selected from one of SEQ.ID.NOS. 258 to 271;
(d) Cys-A5 is selected from SEQ.ID.NOS. 272 and 273;
(e) Cys-A6 is selected from SEQ.ID.NOS. 274 to 276;
(f) Cys-A7-Cys-A8 is selected from one of SEQ.ID.NOS. 277 to 279;
(g) Cys-A9 is selected from one of SEQ.ID.NOS. 280 to 282; and
(h) Cys-A10 is selected from one of SEQ.ID.NOS. 283 to 307.
4. The protein of claim 3, wherein
(a) A3 is selected from the group consisting of
Glu-Ala-Lys,
Glu-Arg-Lys,
Glu-Pro-Lys,
Glu-Lys-Lys,
Glu-Ile-Thr,
Glu-His-Arg,
Glu-Leu-Lys, and
Glu-Thr-Lys;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A7 is Val or Ile;
(d) A8 includes an amino acid sequence selected from the group consisting of

A8.sub.a -A8.sub.b -Gly-Phe-Tyr-Arg-Asp [SEQ. ID. NO. 75],
A8.sub.a -A8.sub.b -Gly-Phe-Tyr-Arg-Asn [SEQ. ID. NO. 76],
A8.sub.a -A8.sub.b -Gly-Tyr-Tyr-Arg-Asp [SEQ. ID. NO. 77],
A8.sub.a -A8.sub.b -Gly-Tyr-Tyr-Arg-Asn [SEQ. ID. NO. 78], and
A8.sub.a -A8.sub.b -Gly-Leu-Tyr-Arg-Asp [SEQ. ID. NO. 79],
wherein at least one of A.sup.8.sub.a and A8.sub.b is Glu or Asp;
(e) A9 is an amino acid sequence of five amino acid residues; and
(f) A10 includes an amino acid sequence selected from the group consisting of
Glu-Ile-Ile-His-Val [SEQ. ID. NO. 74],
Asp-Ile-Ile-Met-Val [SEQ. ID. NO. 75],
Phe-Ile-Thr-Phe-Ala-Pro [SEQ. ID. NO. 76], and
Met-Glu-Ile-Ile-Thr [SEQ. ID. NO. 77].
5. The protein of claim 4 having a NAP domain substantially the same as a NAP domain selected from the group consisting of AcaNAP5 [SEQ. ID. NO. 40], AcaNAP6 [SEQ. ID. NO. 41], AcaNAP48 [SEQ. ID. NO. 42], AcaNAP23 [SEQ. ID. NO. 43], AcaNAP24 [SEQ. ID. NO. 44], AcaNAP25 [SEQ. ID. NO. 45], AcaNAP44 [SEQ. ID. NO. 46], AcaNAP31 [SEQ. ID. NO. 47], AceNAP4 [SEQ. ID. NO. 48 or 49], AcaNAP45 [SEQ. ID. NO. 50 or 53], AcaNAP47 [SEQ. ID. NO. 51 or 54], AduNAP7 [SEQ. ID. NO. 52 or 56], AduNAP4 [SEQ. ID. NO. 55], AceNAP5 [SEQ. ID. NO. 57], and AceNAP7 [SEQ. ID. NO. 58].
6. An isolated protein having anticoagulant activity and having one or more NAP domains, wherein each NAP domain includes the sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10 (FORMULA V),
wherein
(a) A1 is an amino acid sequence of 7 to 8 amino acid residues;
(b) A2 is an amino acid sequence;
(c) A3 is an amino acid sequence of 3 amino acid residues;
(d) A4 is an amino acid sequence;
(e) A5 is an amino acid sequence of 3 to 4 amino acid residues;
(f) A6 is an amino acid sequence;
(g) A7 is an amino acid residue;
(h) A8 is an amino acid sequence of 11 to 12 amino acid residues;
(i) A9 is an amino acid sequence of 5 to 7 amino acid residues; and
(j) A10 is an amino acid sequence;
wherein each A2, A4, A6 and A10 has an independently selected number of independently selected amino acid residues and each sequence is selected such that each NAP domain has in total less than about 120 amino acid residues, and wherein said NAP domain includes the amino acid sequence:
Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys-A10,
wherein
(a) Cys-A1 is selected from SEQ.ID.NOS. 87 and 309;
(b) Cys-A2-Cys is selected from one of SEQ.ID.NOS. 309 to 311;
(c) A3-Cys-A4 is selected from one of SEQ.ID.NOS. 312 to 325;
(d) Cys-A5 is selected from SEQ.ID.NOS. 326 and 327;
(e) Cys-A6 is selected from one of SEQ.ID.NOS. 328 to 330;
(f) Cys-A7-Cys-A8 is selected from SEQ.ID.NOS. 331 to 332;
(g) Cys-A9 is selected from one of SEQ.ID.NOS. 333 to 335; and
(h) Cys-A10 is selected from one of SEQ.ID.NOS. 336 to 338.
7. An isolated protein of claim 1 wherein A8 has the sequence Glu-A8.sub.a -A8.sub.b wherein A.sup.8.sub.a and A8.sub.b are independently selected amino acid residues.
8. An isolated protein of claim 7 where A8.sub.a is selected from Ala, Arg, Pro, Lys, Ile, His, Leu and Thr and A8.sub.b is selected from Lys, Thr and Arg.
9. An isolated protein of claim 8 wherein A8 is selected from the group consisting of Glu-Ala-Lys, Glu-Arg-Lys, Glu-Pro-Lys, Glu-Lys-Lys, Glu-Ile-Thr, Glu-His-Arg, Glu-Leu-Lys and Glu-Thr-Lys.
10. An isolated protein of claim 1 wherein A4 is an amino acid sequence having a net anionic charge.
11. An isolated protein of claim 1 wherein A7 is Val or Ile.
12. An isolated protein of claim 1 wherein A8 includes the amino acid sequence:
A8.sub.a -A8.sub.b -A8.sub.c -A8.sub.d -A8.sub.e -A8.sub.f -A8.sub.g (SEQ. ID. NO. 0b)
wherein
(a) A8.sub.a is the first amino acid residue in A8; and
(b) at least one of A8.sub.a and A8.sub.b is selected from Glu and Asp; and
(c) A8.sub.c through A.sup.8.sub.g are independently selected amino acid residues.
13. An isolated protein of claim 12 wherein
(a) A8.sub.c is Gly;
(b) A8.sub.d is selected from Phe, Tyr and Leu;
(c) A8.sub.e is Tyr;
(d) A8.sub.f is Arg; and
(e) A8.sub.g is Asp or Asn.

14. An isolated protein of claim 13 wherein A8.sub.c -A8.sub.d -A8.sub.f -A8.sub.g is selected from one of SEQ. ID. NOS. 69 to 73.
15. An isolated protein of claim 1 wherein A10 includes an amino acid sequence selected from one of SEQ. ID. NOS. 74 TO 77.
16. An isolated protein of claim 15 wherein A10 includes SEQ. ID. NO. 74.
17. An isolated protein according to claim 1 wherein
a) A3 has the amino acid sequence Glu-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.b are independently selected amino acid residues;
b) A4 is an amino acid sequence having a net anionic charge;
c) A7 is selected from Val and Ile;
d) A8 includes an amino acid sequence selected from one of SEQ. ID. NOS. 69 to 73; and
e) A10 includes an amino acid sequence selected from one of SEQ. ID. NOS. 74 to 77.
18. An isolated protein according to claim 17 having one or two NAP domains.
19. An isolated protein according to claim 17 having one NAP domain.
20. An isolated protein of claim 1 wherein
(a) A3 is selected from the group consisting of Glu-Ala-Lys, Glu-Arg-Lys, Glu-Pro-Lys, Glu-Lys-Lys, Glu-Ile-Thr, Glu-His-Arg, Glu-Leu-Lys and Glu-Thr-Lys;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A7 is Val or Ile;
(d) A8 includes an amino acid sequence selected from one of SEQ. ID. NOS. 78 to 82;
(e) A9 is an amino acid sequence of five amino acid residues; and
(f) A10 includes an amino acid sequence selected from one of SEQ. ID. NOS. 74 to 77.
21. An isolated protein of claim 20 having one or two NAP domains.
22. An isolated protein of claim 20 having one NAP domain.
23. An isolated protein of claim 1 wherein A3 has the amino acid sequence Asp-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.b are independently selected amino acid residues.
24. An isolated protein of claim 23 wherein A3 is Asp-Lys-Lys.
25. An isolated protein of claim 1 wherein A4 is an amino acid sequence having a net anionic charge.
26. An isolated protein according to claim 1 wherein A5 is A5.sub.a -A5.sub.b -A5.sub.c -A5.sub.d (SEQ. ID. NO. 84) and wherein A5.sub.a through A5.sub.b are independently selected amino acid residues.
27. An isolated protein according to claim 26 wherein A5.sub.a is Leu and A5.sub.c is Arg.
28. An isolated protein according to claim 1 wherein A7 is Val or Ile.
29. An isolated protein according to claim 28 wherein A7 is Val.
30. An isolated protein according to claim 1 wherein A8 includes the amino acid sequence A8.sub.a -A8.sub.b -A8.sub.c -A8.sub.d -A8.sub.e -A8.sub.f -A8.sub.g (SEQ. ID. NO. 69) wherein
(a) A8.sub.a is the first amino acid residue in A8;
(b) at least one of A8.sub.a and A8.sub.b is selected from Glu and Asp; and
(c) A8.sub.c through A.sup.8.sub.g are independently selected amino acid residues.
31. An isolated protein according to claim 30 wherein
(a) A8.sub.c is Gly;
(b) A8.sub.d is selected from Phe, Tyr and Leu;
(c) A8.sub.e is Tyr;
(d) A8.sub.f is Arg; and
(e) A.sup.8.sub.g is selected from Asp and Asn.
32. An isolated protein according to claim 31 wherein A8.sub.c -A8.sub.d -A8.sub.e -A8.sub.f -A8.sub.g is SEQ. ID. NO. 70.
33. An isolated protein of claim 1 wherein
(a) A3 has the amino acid sequence Asp-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.b are independently selected amino acid residues;
b) A4 is an amino acid sequence having a net anionic charge;
(c) A5 has the amino acid sequence A5.sub.a -A5.sub.b -A5.sub.c -A5.sub.d (SEQ. ID. NO. 85) wherein A5.sub.a through A5.sub.d are independently selected amino acid residues; and
(d) A7 is selected from Val and Ile.
34. An isolated protein of claim 33 having one or two NAP domains.
35. An isolated protein of claim 33 having one NAP domain.
36. An isolated protein of claim 1 in wherein
a) A3 is Asp-Lys-Lys;
b) A4 is an amino acid sequence having a net anionic charge;
(c) A5 has the amino acid sequence A5.sub.a -A5.sub.b -A5.sub.c -A5.sub.d (SEQ. ID. NO. 85) wherein A5.sub.a through A5.sub.d are independently selected amino acid residues;
(d) A7 is Val; and

(e) A8 includes the amino acid sequence A8.sub.a -A8.sub.b -Gly-Phe-Tyr-Arg-Asn (SEQ. ID. NO. 79) wherein at least one of A8.sub.a and A8.sub.b is Glu or Asp.
37. An isolated protein of claim 36 having one or two NAP domains.
38. An isolated protein of claim 36 having one NAP domain.
39. An isolated protein of claim 3 wherein A3 has the amino acid sequence Glu-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.b are independently selected amino acid residues.
40. An isolated protein of claim 39 wherein A3 is Glu-Pro-Lys.
41. An isolated protein of claim 3 wherein A4 has a net anionic charge.
42. An isolated protein of claim 3 wherein A5 has the amino acid sequence A5.sub.a -A5.sub.b -A5.sub.c wherein A.sup.5.sub.a through A5.sub.c are independently selected amino acid residues.
43. An isolated protein of claim 42 wherein A.sup.5.sub.a is Thr and A5.sub.c is Asn.

44. An isolated protein of claim 43 wherein A5 is Thr-Leu-Asn or Thr-Met-Asn.
45. An isolated protein of claim 3 wherein A7 is Glu.
46. An isolated protein of claim 3 wherein
(a) A3 has the sequence of Glu-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.b are independently selected amino acid residues;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A5 has the sequence A5.sub.a -A5.sub.b -A5.sub.c wherein A5.sub.a to A5.sub.c are independently selected amino acid residues; and
(d) A7 is Glu.
47. An isolated protein of claim 46 having one or two NAP domains.
48. An isolated protein of claim 46 having one NAP domain.
49. An isolated protein of claim 3 wherein
(a) A3 is Glu-Pro-Lys;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A5 is selected from Thr-Leu-Asn and Thr-Met-Asn; and
(d) A7 is Glu.
50. An isolated protein of claim 49 having one or two NAP domains.
51. An isolated protein of claim 49 having one NAP domain.
52. An isolated protein of claim 6 wherein A3 has the sequence Glu-A3.sub.a -A3.sub.b wherein A3.sub.a and A3.sub.b are independently selected amino acid residues.
53. An isolated protein of claim 52 wherein A3.sub.a is selected from Ala, Arg, Pro, Lys, Ile, His, Leu and Thr and A3.sub.b is selected from Lys, Thr and Arg.
54. An isolated protein of claim 53 wherein A3 is selected from Glu-Ala-Lys, Glu-Arg-Lys, Glu-Pro-Lys, Glu-Lys-Lys, Glu-Ile-Thr, Glu-His-Arg, Glu-Leu-Lys and Glu-Thr-Lys.
55. An isolated protein of claim 6 wherein A4 is an amino acid sequence having a net anionic charge.
56. An isolated protein of claim 6 wherein A7 is Val or Ile.
57. An isolated protein of claim 6 wherein A8 includes the amino acid sequence A8.sub.a -A8.sub.b -A8.sub.c -A8.sub.d -A8.sub.e -A8.sub.f -A8.sub.g (SEQ. ID. NO. 66) wherein
(a) A8.sub.a is the first amino acid in A8;
(b) at least one of A8.sub.a and A8.sub.b is selected from Glu and Asp; and
(c) A8.sub.c and A8.sub.g are independently selected amino acid residues.
58. An isolated protein of claim 57 wherein
(a) A8.sub.c is Gly;
(b) A8.sub.d is selected from Phe, Tyr and Leu;
(c) A8.sub.e is Tyr;
(d) A8.sub.f is Arg; and
(e) A8.sub.g is selected from Asp and Asn.
59. An isolated protein of claim 58 wherein A8.sub.c -A8.sub.d -A8.sub.e -A8.sub.f -A8.sub.g is selected from SEQ. ID. NOS. 69 to 73.
60. An isolated protein of claim 6 wherein A10 includes an amino acid sequence selected from SEQ. ID. NOS. 74 to 77.
61. An isolated protein of claim 6 wherein
(a) A3 has the amino acid sequence Glu-A3.sub.a -A3.sub.b wherein A.sup.3.sub.a and A3.sub.b are independently selected amino acid residues;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A7 is selected from Val and Ile;
(d) A8 includes an amino acid sequence selected from SEQ. ID. NOS. 69 to 73; and
(e) A10 includes an amino acid sequence selected from SEQ. ID. NOS. 74 to 77.
62. An isolated protein of claim 61 having one or two NAP domains.
63. An isolated protein of claim 61 having one NAP domain.
64. An isolated protein of claim 61 having two NAP domains.

65. An isolated protein of claim 6 wherein
(a) A3 is selected from Glu-Ala-Lys, Glu-Arg-Lys, Glu-Pro-Lys, Glu-Lys-Lys, Glu-Ile-Thr, Glu-His-Arg, Glu-Leu-Lys and Glu-Thr-Lys;
(b) A4 is an amino acid sequence having a net anionic charge;
(c) A7 is Val or Ile;
(d) A8 includes an amino acid sequence selected one of SEQ. ID. NOS. 78 to 82;
(e) A9 is an amino acid sequence having five amino acid residues; and
(f) A10 includes an amino acid sequence selected from one of SEQ. ID. NOS. 74 to 77.
66. An isolated protein of claim 65 having one or two NAP domains.
67. An isolated protein of claim 65 having one NAP domain.
68. An isolated protein of claim 65 having two NAP domains.
69. An isolated protein having anticoagulant and/or serine protease inhibitory activity and having one or more NAP domains, wherein each NAP domain includes the sequence Cys-A.sub.1 -Cys-A.sub.2 -Cys-A.sub.3 -Cys-A.sub.4 -Cys-A.sub.5 -Cys-A.sub.6 -Cys-A.sub.7 -Cys-A.sub.8 -Cys-A.sub.9 -Cys [FORMULA 17], wherein
(a) A.sub.1 is an amino acid sequence containing 7 to 8 amino acid residues;
(b) A.sub.2 is an amino acid sequence containing 4 to 5 amino acid residues;
(c) A.sub.3 is an amino acid sequence containing 3 amino acid residues;
(d) A.sub.4 is an amino acid sequence containing 6 to 7 amino acid residues;
(e) A.sub.5 is an amino acid sequence containing 3 to 4 amino acid residues;
(f) A.sub.6 is an amino acid sequence containing 3 to 5 amino acid residues;
(g) A.sub.7 is an amino acid residue;
(h) A.sub.8 is an amino acid sequence containing 10 to 12 amino acid residues; and
(i) A.sub.9 is an amino acid sequence containing 5 to 6 amino acid residues;
and wherein said NAP domain includes the amino acid sequence Cys-A1-Cys-A2-Cys-A3-Cys-A4-Cys-A5-Cys-A6-Cys-A7-Cys-A8-Cys-A9-Cys, wherein
(a) Cys-A1 is selected from SEQ. ID. NOS. 66 and 129;
(b) Cys-A2-Cys is selected from one of SEQ. ID. NOS. 130 to 133;
(c) A3-Cys-A4 is selected from one of SEQ. ID. NOS. 134 to 145;
(d) Cys-A5 is selected from one of SEQ. ID. NOS. 146 and 147;
(e) Cy-A6 is selected from one of SEQ. ID. NOS. 148 to 150;
(f) Cys-A7-Cys-A8 is selected from one of SEQ. ID. NOS. 151 to 153; and
(g) Cys-A9-Cys is selected from SEQ. ID. NOS. 154 and 155.
70. An isolated protein of claim 69 wherein
(a) Cys-A2-Cys is selected from SEQ. ID. NOS. 131 and 131; and
(b) A3-Cys-A4 is selected from one of SEQ. ID. NOS. 135 to 145.
71. An isolated protein of claim 71 having a NAP domain wherein
(a) SEQ. ID. NOS. 66 and 129 have Glu at location 9;
(b) SEQ. ID. NOS. 130 and 131 have Gly at location 8;
(c) SEQ. ID. NOS. 151 to 153 have Gly at location 6 and Arg at location 9; and
(d) SEQ. ID. NOS. 154 and 155 have Val at location 2.
72. An isolated protein of claim 71 having a NAP domain wherein SEQ. ID. NOS. 151 to 153 have an amino acid sequence which includes (a), (b) and/or (c) wherein
(a) is Val or Glu at location 2;
(b) is Leu or Phe at location 7; and
(c) is Lys or Tyr at location 8.
73. An isolated protein of claim 71 having a NAP domain wherein
(a) SEQ. ID. NO. 151 has Asp or Gly at location 14;
(b) SEQ. ID. NO. 152 has Asp or Gly at location 13; and
(c) SEQ. ID. NO. 153 has Gly at location 13.